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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 03/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/724,000	POLVERINO ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,13,14,16,46,47,57 and 59-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,13,14,16,46,47,57 and 59-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *20060320* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Copy of a memorandum by Dr. A.P. Patterson, dated January 14, 2003; pp. 1-3.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 21, 2005, has been entered.

1. The amendment filed December 21, 2005, has been entered. Claim 61 has been amended.

2. Claims 9, 13, 14, 16, 46, 47, 57, and 59-61 are pending in the application.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. The indicated allowability of claims 9, 13, 16, 57, 59, and 60 is withdrawn in view of the newly discovered references teaching subject matter that anticipates those claims or after further consideration, in view of the written description and enablement requirements set forth under 35 U.S.C. 112, first paragraph. New grounds of rejection follow.

Claim Rejections - 35 USC § 112

5. Claims 9, 13, 14, 16, 46, 47, 57, and 59-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for

Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description'' Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement (66 FR 1099-1111, January 5, 2001) states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). "Guidelines" further states, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant had possession of the claimed invention at the time the application was filed.

Claim 9 is drawn to a genus of polypeptides having (i.e., comprising) *an* amino acid sequence as set forth in SEQ ID NO: 5, which is produced by the recited process. *An* amino acid sequence of SEQ ID NO: 5 is any sequence of two or more contiguous amino acids of that sequence. Accordingly, claim 9 is drawn to a genus of structurally and functionally disparate polypeptides that are merely required to have amino acid sequences that commonly share at least two or more contiguous amino acids of the amino acid sequence of SEQ ID NO: 5. Given the substantial variability of the members of the genus to which the claim is directed, the polypeptide

of SEQ ID NO: 5 is not deemed representative of the genus, as a whole, and moreover the skilled artisan could not immediately envision, recognize, or distinguish at least a substantial number of the members of the genus.

Claim 13 is similarly drawn to a genus of structurally and functionally different polypeptides, which merely comprise an amino acid sequence of SEQ ID NO: 5. Again, given the substantial variability of the members of the genus to which the claim is directed, the polypeptide of SEQ ID NO: 5 is not deemed representative of the genus, as a whole, and moreover the skilled artisan could not immediately envision, recognize, or distinguish at least a substantial number of the members of the genus.

In the alternative, claim 13 is drawn to a genus of structurally and functionally different polypeptides, which merely comprise an amino acid sequence encoded by a DNA insert encoding a Secs-1 polypeptide, which is contained in ATCC Deposit No. PTA-1755. The claimed polypeptide is not necessarily the Secs-1 polypeptide, nor does it necessarily have an amino acid sequence comprising the full-length amino acid sequence of the Secs-1 polypeptide. Furthermore, as addressed in preceding Office actions, there is no clear nexus between the amino acid sequence of SEQ ID NO: 5 and the amino acid sequence of the Secs-1 polypeptide encoded by the DNA insert contained in ATCC Deposit No. PTA-1755. Consequently, claim 13 encompasses polypeptides encoded by a DNA insert contained in the deposited material, which encodes "a Secs-1 polypeptide", but which do not necessarily bear any structural relationship to the polypeptide of SEQ ID NO: 5. This position is supported by the disclosure at page 12 of the specification, which describes "a Secs-1 polypeptide" as a polypeptide comprising the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 5, or polypeptides related thereto, including fragments, orthologs, variants, and derivatives possessing at least one activity of a Secs-1 polypeptide. Given such a disclosure, it is apparent that claim 13 is directed a genus of polypeptides that may differ substantially both in terms of their structures and their functions. There is no disclosure of any particularly identifying (i.e., substantial) structural feature that is shared by each and every one of the proteins encompassed by the claim and any particularly identifying functional feature that correlates with the presence of such a structural feature, which is necessarily shared by at least most of these proteins. Therefore, as the polypeptide of SEQ ID NO: 5 is not deemed representative of the genus, as a whole, the skilled artisan could not

immediately envision, recognize, or distinguish at least a substantial number of the members of the genus.

Claim 14 is similarly drawn to a genus of structurally and functionally disparate polypeptides. For example, claim 14, which is directed to any polypeptide comprising a fragment of at least about 25 amino acid residues of SEQ ID NO: 5, encompasses any polypeptide having an amino acid sequence comprising at least 25 contiguous amino acids of SEQ ID NO: 5, but which does not necessarily bear any greater structural relationship to the polypeptide of SEQ ID NO: 5 or share any one of its functions. For this reason, the skilled artisan could not immediately envision, recognize, or distinguish at least a substantial number of the members of the genus.

Claim 57 is drawn to a polypeptide produced by a process; the polypeptide is not required to have any particular structure or function, so long as it may be produced by the recited process. In other words, claim 57 is not directed solely to a polypeptide comprising, for example, the amino acid sequence of SEQ ID NO:" 5, but to any polypeptide produced by a host cell containing a vector comprising a nucleic acid molecule having a nucleotide sequence of a region of the nucleotide sequence of SEQ ID NO: 4. Notably, the host cell to which the claim is directed need not comprise a vector comprising a nucleotide sequence encoding the polypeptide of SEQ ID NO: 5, for example, as it must merely comprise a *region* of such a nucleotide sequence. As such, the skilled artisan could not immediately envision, recognize, or distinguish at least a substantial number of the members of the genus.

All of the other claims, which have not been specifically mentioned above, fail to satisfy the written description requirement for the same or analogous reasons.

In each instance, where the skilled artisan could not immediately envision, recognize, or distinguish at least a substantial number of the members of the claimed genus of polypeptide, the disclosure of the presently claimed invention would not be sufficient to reasonably convey to the skilled artisan that Applicant had possession of that claimed subject matter at the time the application was filed.

6. Claims 46 and 47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** an isolated fusion polypeptide

comprising the amino acid sequence of SEQ ID NO: 5 and a heterologous amino acid sequence, and an isolated fusion polypeptide comprising the amino acid sequence of SEQ ID NO: 6, optionally comprising an additional amino-terminal methionine, and a heterologous amino acid sequence, **does not reasonably provide enablement for making and using** any of such fusion polypeptides, which are not isolated. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue experimentation.

As the claims are specifically fusion polypeptides, which are not necessarily isolated, the claims are broadly but reasonably interpreted to read on polypeptides that are comprised within the cells of an organism (e.g., a human patient) that has been treated using any of the disclosed

recombinant genetic processes termed in the art as "gene therapy". Such disclosures are found throughout the specification; see, e.g., pages 71, 76, 77, 79-81, and 85.

The art of gene therapy, i.e., the *in vivo* delivery genetic information to targeted cells within a body using naked DNA or viral vectors or by reintroducing *ex vivo* modified host cells into the body, is still in its infancy. Moreover, the art is highly unpredictable and its successful application has been hindered by numerous limitations, which the specification does not remedy and would preclude the skilled artisan from having a reasonable expectation of successfully making and using the claimed invention without undue experimentation.

For example, the teachings of the specification have not overcome the problems with *in vivo* delivery and expression. Verma et al. (*Nature* 1997, **389**: 239-242) teaches that the Achilles heel of gene therapy is gene delivery (page 239, column 3). Verma et al. states that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression; see entire document (e.g., page 239, column 3). Similarly, Amalfitano et al. (*Current Gene Therapy* 2002, **2**: 111-133) teaches that non-viral mediated transfer of DNA generally suffers from low transduction efficiencies; see entire document (e.g., page 111, column 2). In addition, Amalfitano et al. discusses numerous limitations that have been encountered in using retroviral vectors to deliver DNA into a subject and teaches the use of adenoviral vectors can be ineffective because of the induction of strong immune responses in the host to the viral vectors and direct acute and chronic toxicity caused by the vector itself; see entire document (e.g., abstract).

It is noted that Amalfitano et al. teaches that a despite general lack of success, the first conclusive evidence that gene therapy can show efficacy in humans was achieved in human X-linked SCID subjects *via* retrovirus transduction (page 111, column 2). However, since the publication, The Department of Health and Human Services has released a memorandum dated January 14, 2003, a copy of which is attached to this Office action, that urges all such investigations to be discontinued until new data are available, the possible etiology and risks of adverse events associated are considered, and recommendations emerge. Despite the initial promise of the trial studying gene transfer as a possible treatment for the disease, investigators have found that retroviral-mediated insertion of the transgene has caused the subjects to develop cancer. The results of the trial underscore the high degree of unpredictability associated with the art and the fact that the skilled artisan could not make or use the claimed invention with a

reasonable expectation of success without need to perform additional and an undue amount of experimentation.

The state of the art, as a whole, is well defined by Pandha et al. (*Current Opinion in Investigational Drugs* 2000; **1** (1): 122-134). Pandha et al. teaches:

> Despite the rapid technological advances that continue to sustain the field of cancer gene therapy, few individual patients have benefited from the revolution so far. The plethora of clinical trials described confirms that each malignancy will have its own ideal strategy based on the associated molecular defects, and there has been rapid progress from this viewpoint. At the same time, there has been a renewed appreciation for the limitations to gene therapy, which include low efficiency of gene transfer, poor specificity of response and methods to accurately evaluate responses, and lack of truly tumor-specific targets at which to aim. As with all new therapies, we are climbing a steep learning curve in terms of encountering treatment-related toxicities, as well as profound ethical and regulatory issues (abstract).

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

This issue may be remedied by amending claim 46 to recite the limitation "isolated" before "fusion polypeptide".

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 9, 13, 14, 16, 46, 47, 57, and 59-61 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent Application Publication No. 2002/0068319 A1.

For clarity, claims 9 and 13 are drawn to isolated polypeptides having the amino acid sequence of SEQ ID NO: 5. Claim 14 is drawn to an isolated polypeptide comprising an amino acid sequence as set forth in SEQ ID NO: 6, optionally comprising an amino-terminal methionine residue, or an isolated polypeptide comprising a fragment of at least about 25 amino acid residues, but not more than 80 amino acid residues, of the amino acid sequence of SEQ ID NO: 5. As explained above, an amino acid sequence of SEQ ID NO: 6 is any sequence of two or more contiguous amino acids of that sequence; as such, claim 6 is drawn to an isolated polypeptide that comprises at least two contiguous amino acid sequences of SEQ ID NO: 6. Furthermore, a polypeptide comprising the amino acid sequence of SEQ ID NO: 5, for example, *comprises* a fragment of at least about 25 amino acid residues, but not more than 80 amino acid residues, of the amino acid sequence of SEQ ID NO: 5. Claim 16 is drawn to an isolated polypeptide encoded by a nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide having an amino acid sequence as set forth in SEQ ID NO: 5. Claim 16 encompasses an isolated polypeptide having an amino acid sequence as set forth in SEQ ID NO: 5. Claims 57, 59, and 60 are, here, drawn to a polypeptide comprising the amino acid sequence of SEQ ID NO: 5, which, absent a showing otherwise, is produced by the recited process. Claim 61 is drawn to a isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 5.

U.S. Patent Application Publication No. 2002/0068319 A1 (Ni et al.) teaches a secreted polypeptide that is identical to the polypeptide of SEQ ID NO: 5; see entire document (e.g., SEQ ID NO: 96 of the Sequence Listing). In addition, Ni et al. teaches the disclosed polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein; see, e.g., paragraph [0429]. For example, Ni et al. discloses fusion proteins comprising the polypeptide that is identical to the polypeptide of SEQ ID NO: 5 and the constant domain of immunoglobulins or fragments thereof; see, e.g., paragraph [0488].

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 14, 57, and 59-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Application Publication No. 2002/0068319 A1.

Here, in the interest of providing compact prosecution, claims 14, 57, and 59-61 are drawn to a polypeptide consisting of a fragment of at least about 25 amino acid residues, but not more than 80 amino acid residues, of the amino acid sequence of SEQ ID NO: 5.

U.S. Patent Application Publication No. 2002/0068319 A1 (Ni et al.) teaches that which is set forth in the above rejection of claims 9, 13, 14, 16, 46, 47, 57, and 59-61 under 35 U.S.C. § 102(e).

Ni et al. does not expressly teach a polypeptide consisting of a fragment of at least about 25 amino acid residues, but not more than 80 amino acid residues, of the amino acid sequence of the polypeptide that comprises an amino acid sequence that is identical to SEQ ID NO: 5.

Nonetheless, Ni et al. teaches polypeptides comprising, or alternatively consisting of, one or more immunogenic epitopes of the polypeptide having the amino acid sequence shown in SEQ ID NO: 96, including, for example, the fragments comprising residues Thr-22 to Cys-40 or Val-44 to His-56; see paragraph [0202].

The largest of the exemplified fragments of the polypeptide of SEQ ID NO: 96 is 19 amino acids in length. 19 may or may not be, arguably, about 25; but even so, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to make a polypeptide consisting of a fragment of about 25 amino acids of the disclosed amino acid sequence that is identical to the amino acid sequence set forth in the instant application as SEQ ID NO: 5. One ordinarily skilled in the art at the time the invention was made would have been motivated to make such polypeptides because, for example, they are used as immunogens to produce a reagent antibodies that bind specifically to the intact polypeptide.

Conclusion

11. No claim is allowed.

12. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. U.S. Patent Application Publication Nos. 2003/0004311, 2003/0017563, 2003/0022239, 2003/0022328, 2003/0022331 each teach a secreted polypeptide comprising an amino acid sequence that is identical to SEQ ID NO: 5.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1643

slr
March 20, 2006